

IN THE CLAIMS:

Please amend the claims to read as set forth in the history of claims, as follows:

1. (Canceled)
2. (Original) An attenuated tumor-targeted bacteria comprising one or more nucleic acid molecules encoding one or more primary effector molecules and one or more secondary effector molecules operably linked to one or more promoters, wherein said attenuated tumor-targeted bacteria is a facultative aerobe or facultative anaerobe.
3. (Canceled)
4. (Canceled)
5. (Currently Amended) ~~The~~ An attenuated tumor-targeted bacteria of ~~claim 2~~ comprising one or more nucleic acid molecules encoding one or more primary effector molecules and one or more secondary effector molecules operably linked to one or more promoters, wherein said attenuated tumor-targeted bacteria is a facultative aerobe or facultative anaerobe and at least one of the primary effector molecules is an anti-angiogenic factor.
6. (Currently Amended) The attenuated tumor-targeted bacteria of claim 5, wherein the anti-angiogenic factor is endostatin, angiostatin, anti-angiogenic antithrombin III, the 29 kDa N-terminal proteolytic fragment of fibronectin, ~~and~~ a 40 kDa C-terminal proteolytic ~~fragments~~ fragment of fibronectin, a uPA receptor antagonist, the 16 kDa proteolytic fragment of prolactin, the 7.8 kDa proteolytic fragment of platelet factor-4, the anti-angiogenic 24 amino acid fragment of platelet factor-4, the anti-angiogenic factor designated 13.40, the anti-angiogenic 22 amino acid peptide fragment of thrombospondin I, the anti-angiogenic 20 amino acid peptide fragment of SPARC, an RGD containing peptide ~~and an~~ NGR containing ~~peptides~~ peptide, ~~the a~~ small anti-angiogenic ~~peptides~~ peptide of laminin, a small anti-angiogenic peptide of fibronectin, a small anti-angiogenic peptide of procollagen, and a small anti-angiogenic peptide of EGF, apomigren, and a peptide ~~antagonists~~ antagonist of integrin $\alpha_v\beta_3$, or a peptide antagonist of VEGF receptor.
7. (Previously Presented) The attenuated tumor-targeted bacteria of claim 2, wherein at least one of the primary effector molecules is a bacteriocin family member with the proviso said bacteriocin is not BRP.
8. (Original) The attenuated tumor-targeted bacteria of claim 7, wherein the bacteriocin family member is ColE1, ColE1a, ColE1b ColE2, ColE3, ColE4,

ColE5, ColE6, ColE7, ColE8, ColE9, Colicin A, Colicin K, Colicin L, Colicin M, cloacin DF13, pesticin A1122, staphylococcin 1580, butyricin 7423, pyocin R1 or AP41, megacin A-216, vibriocin, or microcin M15.

9. (Withdrawn) The attenuated tumor targeted bacteria of claim 2, wherein at least one of the primary effector molecules is a tumor inhibitory enzyme.

10. (Withdrawn) The attenuated tumor targeted bacteria of claim 9, wherein the tumor inhibitory enzyme is methionase, asparaginase, lipase, phospholipase, protease, DNAase or glycosidase.

11. (Withdrawn) The attenuated tumor targeted bacteria of claim 2, wherein at least one of the primary effector molecules is hemolysin, verotoxin, CNF1, CNF2, or PMT.

12. (Previously Presented) The attenuated tumor-targeted bacteria of claim 2, wherein at least one of the primary effector molecules is derived from an animal, plant, bacteria, or virus.

13. (Withdrawn) The attenuated tumor-targeted bacteria of claim 2, wherein at least one of the secondary effector molecules is an immunomodulating agent, an anti-tumor protein, a pro-drug converting enzyme, an antisense molecule, a ribozyme, or an antigen.

14. (Previously Presented) The attenuated tumor-targeted bacteria of claim 2, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

15. (Canceled)

16. (Previously Presented) The attenuated tumor-targeted bacteria of claim 2, wherein at least one of the secondary effector molecules is a bacteriocin release factor (BRP).

17.-25. (Canceled)

26. (Original) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an attenuated tumor-targeted bacteria comprising one or more nucleic acid molecules encoding one or more primary effector molecules and one or more secondary effector molecules operably linked to one or more promoters, wherein said attenuated tumor-targeted bacteria is a facultative aerobe or facultative anaerobe.

27. (Canceled)

28. (Canceled)

29. (Currently Amended) ~~The A~~ pharmaceutical composition of claim 26 comprising a pharmaceutically acceptable carrier and an attenuated tumor-targeted bacteria comprising one or more nucleic acid molecules encoding one or more primary effector molecules and one or more secondary effector molecules operably linked to one or more promoters, wherein said attenuated tumor-targeted bacteria is a facultative aerobe or facultative anaerobe and at least one of the primary effector molecules is an anti-angiogenic factor.

30. (Currently Amended) The pharmaceutical composition of claim 29, wherein the anti-angiogenic factor is endostatin, angiostatin, anti-angiogenic antithrombin III, the 29 kDa N-terminal proteolytic fragment of fibronectin, and a 40 kDa C-terminal proteolytic fragments fragment of fibronectin, a uPA receptor antagonist, the 16 kDa proteolytic fragment of prolactin, the 7.8 kDa proteolytic fragment of platelet factor-4, the anti-angiogenic 24 amino acid fragment of platelet factor-4, the anti-angiogenic factor designated 13.40, the anti-angiogenic 22 amino acid peptide fragment of thrombospondin I, the anti-angiogenic 20 amino acid peptide fragment of SPARC, an RGD containing peptide and an NGR containing peptides peptide, the a small anti-angiogenic peptides peptide of laminin, a small anti-angiogenic peptide of fibronectin, a small anti-angiogenic peptide of procollagen, and a small anti-angiogenic peptide of EGF, apomigren, and a peptide antagonists antagonist of integrin $\alpha_v\beta_3$, or a peptide antagonist of VEGF receptor.

31. (Previously Presented) The pharmaceutical composition of claim 26, wherein at least one of the primary effector molecules is a bacteriocin family member with the proviso said bacteriocin is not BRP.

32. (Original) The pharmaceutical composition of claim 31, wherein the bacteriocin family member is ColE1, ColE1a, ColE1b ColE2, ColE3, ColE4, ColE5, ColE6, ColE7, ColE8, ColE9, Colicin A, Colicin K, Colicin L, Colicin M, cloacin DF13, pesticin A1122, staphylococcin 1580, butyricin 7423, pyocin R1 or AP41, megacin A-216, vibriocin or microcin M15.

33. (Withdrawn) The pharmaceutical composition of claim 26, wherein at least one of the primary effector molecules is a tumor inhibitory enzyme.

34. (Withdrawn) The pharmaceutical composition of claim 33, wherein the tumor inhibitory enzyme is methionase, asparaginase, lipase, phospholipase, protease, DNAase or glycosidase.

35. (Withdrawn) The pharmaceutical composition of claim 26, wherein at least one of the primary effector molecules is hemolysin, verotoxin, CNF1, CNF2, or PMT.

36. (Previously Presented) The pharmaceutical composition of claim 26, wherein at least one of the primary effector molecules is derived from an animal, plant, bacteria, or virus.

37. (Withdrawn) The pharmaceutical composition of claim 26, wherein at least one of the secondary effector molecules is an immunomodulating agent, an anti-tumor protein, a pro-drug converting enzyme, an antisense molecule, a ribozyme, or an antigen.

38. (Previously Presented) The pharmaceutical composition of claim 26, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

39. (Canceled)

40. (Previously Presented) The pharmaceutical composition of claim 26, wherein at least one of the secondary effector molecules is a bacteriocin release factor (BRP).

41.-48. (Canceled)

49. (Currently Amended) A method for delivering one or more primary effector molecules and one or more secondary effector molecules ~~for the treatment of~~ to a subject to treat a solid tumor cancer ~~to a subject in need of such treatment~~, comprising administering to said subject a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an attenuated tumor-targeted bacteria comprising one or more nucleic acid molecules encoding one or more primary effector molecules and one or more secondary effector molecules operably linked to one or more promoters, wherein said attenuated tumor-targeted bacteria is a facultative aerobe or facultative anaerobe.

50. (Canceled)

51. (Canceled)

52. (Currently Amended) ~~The A method of claim 49 for delivering one or more primary effector molecules and one or more secondary molecules to a subject to treat a solid tumor cancer~~, comprising administering to said subject a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an attenuated tumor-targeted bacteria comprising one or more nucleic acid molecules encoding one or more primary effector molecules and one or more secondary effector molecules operably linked to one or more promoters, wherein said attenuated tumor-targeted bacteria is a facultative aerobe or

facultative anaerobe and at least one of the primary effector molecules is an anti-angiogenic factor.

53. (Currently Amended) The method of claim 52, wherein the anti-angiogenic factor is endostatin, angiostatin, anti-angiogenic antithrombin III, the 29 kDa N-terminal proteolytic fragment of fibronectin, ~~and~~ a 40 kDa C-terminal proteolytic fragments fragment of fibronectin, a uPA receptor antagonist, the 16 kDa proteolytic fragment of prolactin, the 7.8 kDa proteolytic fragment of platelet factor-4, the anti-angiogenic 24 amino acid fragment of platelet factor-4, the anti-angiogenic factor designated 13.40, the anti-angiogenic 22 amino acid peptide fragment of thrombospondin I, the anti-angiogenic 20 amino acid peptide fragment of SPARC, an RGD containing peptide ~~and an~~ NGR containing peptides peptide, ~~the~~ a small anti-angiogenic peptides peptide of laminin, a small anti-angiogenic peptide of fibronectin, a small anti-angiogenic peptide of procollagen, ~~and~~ a small anti-angiogenic peptide of EGF, apomigren, ~~and a~~ peptide antagonists antagonist of integrin $\alpha_v\beta_3$, or a peptide antagonist of VEGF receptor.

54. (Previously Presented) The method of claim 49, wherein at least one of the primary effector molecules is a bacteriocin family member with the proviso said bacteriocin is not BRP.

55. (Original) The method of claim 54, wherein the bacteriocin family member is ColE1, ColE1a, ColE1b ColE2, ColE3, ColE4, ColE5, ColE6, ColE7, ColE8, ColE9, Colicin A, Colicin K, Colicin L, Colicin M, cloacin DF13, pesticin A1122, staphylococcin 1580, butyricin 7423, pyocin R1 or AP41, megacin A-216, vibriocin or microcin M15.

56. (Withdrawn) The method of claim 49, wherein at least one of the primary effector molecules is a tumor inhibitory enzyme.

57. (Withdrawn) The method of claim 56, wherein the tumor inhibitory enzyme is methionase, asparaginase, lipase, phospholipase, protease, DNAase or glycosidase.

58. (Withdrawn) The method of claim 49, wherein at least one of the primary effector molecules is hemolysin, verotoxin, CNF1, CNF2 or PMT.

59. (Previously Presented) The method of claim 49, wherein at least one of the primary effector molecules is derived from an animal, plant, bacteria, or virus.

60. (Withdrawn) The method of claim 49, wherein at least one of the secondary effector molecules is an anti-tumor protein, an immunomodulating agent, a pro-drug converting enzyme, an antisense molecule, a ribozyme, or an antigen.

61. (Previously Presented) The method of claim 49, wherein the attenuated tumor-targeted bacteria is *Salmonella*.
62. (Canceled)
63. (Original) The method of claim 49, wherein at least one of the secondary effector molecules is a bacteriocin release factor.
- 64.-99. (Canceled)
100. (Withdrawn) The attenuated tumor targeted bacteria of claim 2, wherein at least one of the secondary effector molecules is a release factor.
101. (Withdrawn) The attenuated tumor targeted bacteria of claim 13, wherein the antisense molecule is double-stranded or single-stranded DNA, double-stranded or single-stranded RNA, or a triplex molecule.
102. (Withdrawn) The attenuated tumor targeted bacteria of claim 13, wherein the anti-tumor protein is a ribosome inactivating protein.
103. (Withdrawn) The attenuated tumor targeted bacteria of claim 102, wherein the ribosome inactivating protein is saporin, ricin, or abrin.
104. (Withdrawn) The attenuated tumor targeted bacteria of claim 13, wherein the pro-drug converting enzyme is cytochrome p450 NADPH oxidoreductase.
105. (Previously Presented) The attenuated tumor targeted bacteria of claim 16, wherein the BRP protein is obtainable from the cloacin DF13 plasmid.
106. (Withdrawn) The attenuated tumor targeted bacteria of claim 13, wherein the immunomodulating agent is IL-1, IL-2, IL-4, IL-5, IL-10, IL-15, IL-18, endothelial monocyte activating protein-2, GM-CSF, IFN- γ , IFN- α , MIP-3 α , SLC, or MIB-3 β .
107. (Withdrawn) The attenuated tumor targeted bacteria of claim 13, wherein the immunomodulating agent is encoded by an MHC gene.
108. (Withdrawn) The attenuated tumor targeted bacteria of claim 107, wherein the immunomodulatory agent encoded by the MHC gene is HLA-B7.
109. (Withdrawn) The attenuated tumor targeted bacteria of claim 13, wherein the immunomodulating agent is α -1,3-galactosyl transferase.

110. (Withdrawn) The attenuated tumor targeted bacteria of claim 13, wherein the immunomodulating agent is a tumor-associated antigen.

111. (Withdrawn) The attenuated tumor targeted bacteria of claim 110, wherein the tumor-associated antigen is carcinoembryonic antigen (CEA).

112. (Withdrawn) The attenuated tumor targeted bacteria of claim 2, wherein the secondary effector molecule is an inhibitor of inducible nitric oxide synthase or of endothelial nitric oxide synthase.

113. (Withdrawn) The pharmaceutical composition of claim 26, wherein at least one of the secondary effector molecules is a release factor.

114. (Withdrawn) The pharmaceutical composition of claim 37, wherein the antisense molecule is double-stranded or single-stranded DNA, double-stranded or single-stranded RNA, or a triplex molecule.

115. (Withdrawn) The pharmaceutical composition of claim 37, wherein the anti-tumor protein is a ribosome inactivating protein.

116. (Withdrawn) The pharmaceutical composition of claim 115, wherein the ribosome inactivating protein is saporin, ricin, or abrin.

117. (Withdrawn) The pharmaceutical composition of claim 37, wherein the pro-drug converting enzyme is cytochrome p450 NADPH oxidoreductase.

118. (Previously Presented) The pharmaceutical composition of claim 40, wherein the BRP protein is obtainable from cloacin DF13.

119. (Withdrawn) The pharmaceutical composition of claim 37, wherein the immunomodulating agent is IL-1, IL-2, IL-4, IL-5, IL-10, IL-15, IL-18, endothelial monocyte activating protein-2, GM-CSF, IFN- γ , IFN- α , MIP-3 α , SLC, or MIB-3 β .

120. (Withdrawn) The pharmaceutical composition of claim 37, wherein the immunomodulating agent is encoded by an MHC gene.

121. (Withdrawn) The pharmaceutical composition of claim 120, wherein the immunomodulatory agent encoded by the MHC gene is HLA-B7.

122. (Withdrawn) The pharmaceutical composition of claim 37, wherein the immunomodulating agent is α -1,3-galactosyl transferase.

123. (Withdrawn) The pharmaceutical composition of claim 37, wherein the immunomodulating agent is a tumor-associated antigen.

124. (Withdrawn) The pharmaceutical composition of claim 123, wherein the tumor-associated antigen is carcinoembryonic antigen (CEA).

125. (Withdrawn) The pharmaceutical composition of claim 26, wherein the secondary effector molecule is an inhibitor of inducible nitric oxide synthase or of endothelial nitric oxide synthase.

126. (Withdrawn) The method of claim 49, wherein at least one of the secondary effector molecules is a release factor.

127. (Withdrawn) The method of claim 60, wherein the antisense molecule is double-stranded or single-stranded DNA, double-stranded or single-stranded RNA, or a triplex molecule.

128. (Withdrawn) The method of claim 60, wherein the anti-tumor protein is a ribosome inactivating protein.

129. (Withdrawn) The method of claim 128, wherein the ribosome inactivating protein is saporin, ricin, or abrin.

130. (Withdrawn) The method of claim 60, wherein the pro-drug converting enzyme is cytochrome p450 NADPH oxidoreductase.

131. (Previously Presented) The method of claim 63, wherein the BRP protein is obtainable from cloacin DF13.

132. (Withdrawn) The method of claim 60, wherein the immunomodulating agent is IL-1, IL-2, IL-4, IL-5, IL-10, IL-15, IL-18, endothelial monocyte activating protein-2, GM-CSF, IFN- γ , IFN- α , MIP-3 α , SLC, or MIB-3 β .

133. (Withdrawn) The method of claim 60, wherein the immunomodulating agent is encoded by an MHC gene.

134. (Withdrawn) The method of claim 60, wherein the immunomodulatory agent encoded by the MHC gene is HLA-B7.

135. (Withdrawn) The method of claim 60, wherein the immunomodulating agent is α -1,3-galactosyl transferase.

136. (Withdrawn) The method of claim 60, wherein the immunomodulating agent is a tumor-associated antigen.

137. (Withdrawn) The method of claim 136, wherein the tumor-associated antigen is carcinoembryonic antigen (CEA).

138. (Withdrawn) The method of claim 49, wherein the secondary effector molecule is an inhibitor of inducible nitric oxide synthase or of endothelial nitric oxide synthase.

139. (Withdrawn) The attenuated tumor targeted bacteria of claim 13, wherein the pro-drug converting enzyme is cytosine deaminase.

140. (Withdrawn) The pharmaceutical composition of claim 37, wherein the pro-drug converting enzyme is cytosine deaminase.

141. (Withdrawn) The method of claim 60, wherein the pro-drug converting enzyme is cytosine deaminase.

Please add new claims 142-188, as follows:

142. (New) The attenuated tumor-targeted bacteria of claim 5, wherein at least one of the primary effector molecules is a bacteriocin family member with the proviso said bacteriocin is not BRP.

143. (New) The attenuated tumor-targeted bacteria of claim 142, wherein the bacteriocin family member is ColE1, ColE1a, ColE1b ColE2, ColE3, ColE4, ColE5, ColE6, ColE7, ColE8, ColE9, Colicin A, Colicin K, Colicin L, Colicin M, cloacin DF13, pesticin A1122, staphylococcin 1580, butyricin 7423, pyocin R1 or AP41, megacin A-216, vibriocin, or microcin M15.

144. (New) The attenuated tumor-targeted bacteria of claim 5, wherein at least one of the primary effector molecules is derived from an animal, plant, bacteria, or virus.

145. (New) The attenuated tumor-targeted bacteria of claim 5, wherein the anti-angiogenic factor is endostatin.

146. (New) The attenuated tumor-targeted bacteria of claim 5, wherein at least one of the secondary effector molecules is a bacteriocin release factor (BRP).

147. (New) The attenuated tumor-targeted bacteria of claim 145, wherein at least one of the secondary effector molecules is a bacteriocin release factor (BRP).

148. (New) The attenuated tumor-targeted bacteria of claim 146, wherein the BRP protein is obtainable from the cloacin DF13 plasmid.

149. (New) The attenuated tumor-targeted bacteria of claim 147, wherein the BRP protein is obtainable from the cloacin DF13 plasmid.

150. (New) The attenuated tumor-targeted bacteria of claim 5, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

151. (New) The attenuated tumor-targeted bacteria of claim 146, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

152. (New) The attenuated tumor-targeted bacteria of claim 147, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

153. (New) The attenuated tumor-targeted bacteria of claim 150, wherein the *Salmonella* is an *msbB*⁻ *Salmonella* mutant.

154. (New) The attenuated tumor-targeted bacteria of claim 151, wherein the *Salmonella* is an *msbB*⁻ *Salmonella* mutant.

155. (New) The attenuated tumor-targeted bacteria of claim 152, wherein the *Salmonella* is an *msbB*⁻ *Salmonella* mutant.

156. (New) The pharmaceutical composition of claim 29, wherein at least one of the primary effector molecules is a bacteriocin family member with the proviso said bacteriocin is not BRP.

157. (New) The pharmaceutical composition of claim 156, wherein the bacteriocin family member is ColE1, ColE1a, ColE1b, ColE2, ColE3, ColE4, ColE5, ColE6, ColE7, ColE8, ColE9, Colicin A, Colicin K, Colicin L, Colicin M, cloacin DF13, pesticin A1122, staphylococcin 1580, butyricin 7423, pyocin R1 or AP41, megacin A-216, vibriocin or microcin M15.

158. (New) The pharmaceutical composition of claim 29, wherein at least one of the primary effector molecules is derived from an animal, plant, bacteria, or virus.

159. (New) The pharmaceutical composition of claim 29, wherein the anti-angiogenic factor is endostatin.

160. (New) The pharmaceutical composition of claim 29, wherein at least one of the secondary effector molecules is a bacteriocin release factor (BRP).

161. (New) The pharmaceutical composition of claim 159, wherein at least one of the secondary effector molecules is a bacteriocin release factor (BRP).

162. (New) The pharmaceutical composition of claim 160, wherein the BRP protein is obtainable from the cloacin DF13 plasmid.

163. (New) The pharmaceutical composition of claim 161, wherein the BRP protein is obtainable from the cloacin DF13 plasmid.

164. (New) The pharmaceutical composition of claim 29, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

165. (New) The pharmaceutical composition of claim 160, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

166. (New) The pharmaceutical composition of claim 161, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

167. (New) The pharmaceutical composition of claim 164, wherein the *Salmonella* is an *msbB*⁻ *Salmonella* mutant.

168. (New) The pharmaceutical composition of claim 165, wherein the *Salmonella* is an *msbB*⁻ *Salmonella* mutant.

169. (New) The pharmaceutical composition of claim 166, wherein the *Salmonella* is an *msbB*⁻ *Salmonella* mutant.

170. (New) The method of claim 52, wherein at least one of the primary effector molecules is a bacteriocin family member with the proviso said bacteriocin is not BRP.

171. (New) The method of claim 170, wherein the bacteriocin family member is ColE1, ColE1a, ColE1b ColE2, ColE3, ColE4, ColE5, ColE6, ColE7, ColE8,

ColE9, Colicin A, Colicin K, Colicin L, Colicin M, cloacin DF13, pesticin A1122, staphylococcin 1580, butyricin 7423, pyocin R1 or AP41, megacin A-216, vibriocin or microcin M15.

172. (New) The method of claim 52, wherein at least one of the primary effector molecules is derived from an animal, plant, bacteria, or virus.

173. (New) The method of claim 52, wherein the anti-angiogenic factor is endostatin.

174. (New) The method of claim 52, wherein at least one of the secondary effector molecules is a bacteriocin release factor (BRP).

175. (New) The method of claim 173, wherein at least one of the secondary effector molecules is a bacteriocin release factor (BRP).

176. (New) The method of claim 174, wherein the BRP protein is obtainable from the cloacin DF13 plasmid.

177. (New) The method of claim 175, wherein the BRP protein is obtainable from the cloacin DF13 plasmid.

178. (New) The method of claim 52, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

179. (New) The method of claim 174, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

180. (New) The method of claim 175, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

181. (New) The method of claim 178, wherein the *Salmonella* is an *msbB*⁻ *Salmonella* mutant.

182. (New) The method of claim 179, wherein the *Salmonella* is an *msbB*⁻ *Salmonella* mutant.

183. (New) The method of claim 180, wherein the *Salmonella* is an *msbB*⁻ *Salmonella* mutant.

184. (New) The method of claim 52, wherein the solid tumor is a sarcoma or carcinoma.

185. (New) The method of claim 52, wherein the solid tumor is a tumor of the central nervous system, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, glioma, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma, renal cancer, bladder cancer or mesothelioma.

186. (New) The method of claim 52, wherein the subject is a human.

187. (New) The method of claim 174, wherein the subject is a human.

188. (New) The method of claim 175, wherein the subject is a human.